UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,337	12/29/2003	Mark H. Tuszynski	041673-2115	9488

30542 7590 01/19/2005

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,337	TUSZYNSKI, MARK H.	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the Restriction was received on 11/8/2004. Claims 1-17 are pending in the instant application. Applicant's response was missing the first two lines on page 2 making the election unintelligible. In a phone interview on 12/2/2004 Ms. Michelle Sympson agreed to fax another copy of the response to the examiner. This was done and the response of 12/2/2004 forms the basis for the office action below. Applicant elected the subject matter of a β-NGF and an adenovirus vector, with traversal. Claims 1-17 are currently under examination.

Election with Traverse

Applicant's election with traverse of the species of: a β-NGF and an adenovirus vector are acknowledged. Applicant's amendments and arguments have been fully considered and have been found to be persuasive in overcoming the grounds of restriction. The restriction requirement mailed on 9/15/2004 is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1- 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-17 are drawn to any method of delivering any therapeutic neurotrophin to the brain. The claims do not require the neurotrophin to have any structural limitations. The claims are drawn to a genus of neurotrophic compositions that are defined solely by the presence of a therapeutic neurotrophin and the ability to ameliorate a defect, disease or damage of the brain.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/ or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is the requirement that the transgene to be delivered encode a neurotrophin. The specification contemplates several neurotrophins in addition to β-NGF (specification pg. 7); however the specification fails to identify any structural feature or functional element, common to all neurotrophins, and known at the time of filing to ameliorate a defect, disease or damage of the brain. The specification does not describe what specific amino acid sequence(s) or tertiary structural element(s) is/are required in order for a neurotrophin to ameliorate a defect, disease or damage of the brain. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed genus of any method of delivery of any neurotrophin.

The Revised Interim Guidelines state, " when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page

71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for a method of delivery of any therapeutic neurotrophin, other than direct injection of a transgene encoding β-NGF, alone or within cells, into the brain. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for grafting genetically modified fibroblast cells comprising an adeno-associated viral vector expressing NGF intraparenchymally to the basal forebrains of monkeys and increasing expression of p75 in cholinergic neurons in the basal forebrain, does not reasonably provide enablement for a method for delivering a neurotrophin composition comprising a transgene encoding a neurotrophin via various administration routes into one or more sites within the targeted region of a mammalian brain to ameliorate the defective, diseased or damaged cholinergic neuron *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention

commensurate in scope with these claims.

Claims 1-17 are directed to a method for delivery of a therapeutic neurotrophin, such as NGF or NT-3, to targeted defective, diseased or damaged cholinergic neurons in a mammalian brain, wherein the transgene is expressed in, or within 500 um, from a targeted cell, and no more than about 10mm from another delivery site, to ameliorate disease, such as Alzheimer's disease *in vivo*. The specification fails to disclose that vector doses of an AAV vector encoding β-NGF can ameliorate a defect, disease or damage *in vivo*. Further, the working examples only disclose that doses of AAV expressing β-NGF were well tolerated in rat brain *in vivo* and NGF expression was observed. The specification does not disclose any examples describing the direct administration of any vector encoded neurotrophin, other than AAV expressing β-NGF, to any mammal other than a rat. Further, the specification does not describe that AAV expressing β-NGF, or any other viral vector encoded neurotrophin can ameliorate the defect, disease or damage in any mammalian brain.

The claims read on gene therapy by using any vector expressing neurotrophin via various administration routes *in vivo*. However, the specification also does not provide an enabling disclosure for using any vector/promoter combination to express a neurotrophin *in vivo*. Verma et al. states that, the Achilles heel of gene therapy is gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, column 3, paragraph 2}. Marshall concurs, stating that, difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field, and that, many problems must be solved before gene therapy will be useful for more than the rare application {Marshall (1995) Science, Vol.

269, page 1054, column 3, paragraph 2, and page 1055, column 1}. Orkin et al. further states in a report to the NIH that, none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated, and that, while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol {Orkin et al. (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2}. Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the need for appropriate vector/promoter combinations for a particular cell type. In regards to the latter issue, Verma states that, the search for such combinations is a case of trail and error for a given cell type {Verma, (1997) Nature, 389, page 240}. Therefore, for the reasons stated above, a practitioner in the art would be unable to predict that a neurotrophin encoded by any vector would have therapeutic activity in a mammalian brain and would ameliorate a defect disease or damage and thus could not practice the invention wit any vector encoded neurotrophin without extensive and arduous experimentation.

Further, the specification provides working examples showing that administration of genetically modified fibroblast cells comprising an adeno-associated viral vector expressing NGF intraparenchymally to the basal forebrains of monkeys results in increased expression of p75 in cholinergic neurons in the basal forebrain. The specification does not teach how to ameliorate any neurological defect, disease or damage with either a genetically modified cell expressing any neurotrophin, or any vector encoded neurotrophin. Specifically, no evidence is presented how the increased expression of p75 ameliorates any defect, damage or disease, such

as Alzheimer's disease (AD). Rogawski teaches that the definitive cause of AD remains unresolved {Rogawski MA (2004) CNS Spect. 9:6-12; Abstract}. Further, Rogawski teaches that while the impairment of cholinergic neurotransmission may underlie some of the defects in cognition, treatment with Memantine, which is not a cholinesterase inhibitor and does not interact with cholinesterase inhibitors, causes cognitive and functional improvements. In addition, Counts et al. teaches that p75 receptor expression in cholinergic receptors remain stable during the course of AD {Counts et al., (2004) Ann Neurol 56:520-531, Abstract; pg. 526, Figure 3}. Further, Counts et al. teaches that signaling through p75 may actually increase in cholinergic basocortical system in AD (pg. 528, col. 1).

Finally, the specification does not enable a method for the delivery of any therapeutic neurotrophin, other than NGF. The specification does not disclose that any neurotrophin, other than NGF, can ameliorate a defect, disease or damage in the brain. Further, Reichardt et al. teaches that while both NGF and NT-3 signal through TrkA receptors on the axons of developing neurons, only NGF supports survival and differentiation, NT-3 does not {Reichardt et al. (2004) Cell 118:141-3; Abstract; pg. 142, Figure 1}. Given the art taught unpredictability in the signaling effects of different neurotrophins, the lack of teachings in the specification on the administration of any vector encoding any neurotrophin in order to ameliorate any neurological defect, disease or damage to any mammal, except the administration of AAV encoded β-NGF to a rodent brain, the art taught unpredictability in the use of any vector system for gene therapy, the lack of guidance that grafting genetically modified fibroblast cells comprising an adeno-associated viral vector expressing NGF intraparenchymally to the basal forebrains of monkeys can ameliorate any defect, disease, or damage and the teachings in the art that p75 expression is

stable in the AD affected brain, the skilled practitioner in the art would be unable to practice the invention, except as a method for grafting genetically modified fibroblast cells comprising an adeno-associated viral vector expressing NGF intraparenchymally to the basal forebrains of monkeys and increased expression of p75 in cholinergic neurons in the basal forebrain, without extensive and arduous experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the phrase "further contact with the neurotrophin" is vague. The body of the claim does not make it clear what is meant by "further contact with the neurotrophin". Further, it is unclear whether the targeted site is delivered with the neurotrophic composition comprising the transgene and the expressed neurotrophin contacts the targeted site, or the targeted site is delivered with the neurotrophic composition comprising the transgenes and further contacted with a neurotrophin protein that is delivered as part of the composition. Clams 2-17 depend on claim 1.

Claim 9 is indefinite because the metes and bounds of what the applicants mean by "greater than or equal to 3 minutes" cannot be determined. The term "greater than or equal to 3 minutes" encompasses a range of time from 3 minutes until the quantum event signifying the end

of the universe. Further the specification only discloses delivery times of 5-10 minutes (see specification, page 3, lines 9-10) and 3-5 minutes (see specification, page 20, lines 12-13).

Claim 10 is indefinite because the metes and bounds of what the applicants mean by "less than or equal to ten minutes" cannot be determined. The term "less than or equal to ten minutes" encompasses a range of time from zero minutes until 10 minutes. If the delivery time is nonexistent, e.g. zero minutes, the claims are unclear on how the invention is to be performed. Further the specification only discloses delivery times of 5-10 minutes (see specification, page 3, lines 9-10) and 3-5 minutes (see specification, page 20, lines 12-13).

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-17 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-17 of prior U.S. Patent No. 6,683,058. Although the conflicting claims are not identical in language, they are identical in content and scope of the subject matter. This is a double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 11, 12 and 13-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2,3, 4 and 5, of U.S. Patent No. 6,451,306. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claim 1 of U. S. Patent No. 6,451,306 is a species of the broader genus of the claims in the instant application. Specifically claim 1, of the instant application, is to any method of delivering a composition containing a transgene encoded neurotrophin to cholinergic neurons in the mammalian brain, where the transgene is expressed in, or within 500 um from a targeted cell and no more than 10 mm from another delivery site, which broadly encompasses Claim 1 of U.S. Patent No. 6,451,306 that asserts a method of intraparenchymal delivery of a composition comprising cells containing a transgene encoding a neurotrophin to the cholinergic basal primate forebrain, where the cells are engrafted within 500 um from a targeted cell and no more than 5 mm from another grafting site. It is well established that a species of a claimed invention renders the genus obvious. In re Schaumann , 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

In the instant application claim 11 depends on claim 1 so as to limit the treated mammal to a human and the transgene to one encoding human nuerotrophin. Claim 2 of U. S.

Patent No. 6,451,306 provides the same limitation to the primate brain. Claim 11, in the instant application, is rejected since it encompasses the invention of U. S. Patent No. 6,451,306.

In the instant application claim 12 depends on claim 1 so as to limit the neurotrophin to human β-NGF. Claim 3 of U. S. Patent No. 6,451,306 provides the same limitation to the nuerotrophin. Claim 12, in the instant application, is rejected since it encompasses the invention of U. S. Patent No. 6,451,306.

In the instant application claim 13 depends on claim 1 so as to limit the neurotrophin to human NT3. Claim 4 of U. S. Patent No. 6,451,306 provides the same limitation to the nuerotrophin. Claim 12, in the instant application, is rejected since it encompasses the invention of U. S. Patent No. 6,451,306.

In the instant application claim 14 and 15 depend on claim 1 so as to limit the method of delivery to intraparenchymal delivery, claim 14, to the cholinergic basal forebrain, claim 15. Claim 1 of U. S. Patent No. 6,451,306 provides the same limitations on the method of delivery. Claims 14 and 15, in the instant application, are rejected since they encompass the invention of U. S. Patent No. 6,451,306.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Martinez-Serrano et al. { Martinez-Serrano et al. (1995) J. Neuroscience 15:5668-5680}.

Martinez-Serrano et al. provides guidance on a method of administering a therapeutic neurotrophin composition, comprising a neural progenitor cell line transfected with a MMLV

retrovirus encoding a mouse NGF cDNA into the brain of a rodent (pgs. 5669-5671). Further, Martinez-Serrano et al. teaches that the engrafted cells blocked over 90% of the cholinergic cell loss in fimbria-fornix induced lesions (Abstract; pg 5677, Figure 6; pg. 5678, Figure 8). The engrafted cells migrated for a distance of 1-1.5 mm from the implantation sites (Abstract; pg 5674, col. 1, pgph 3) and expressed NGF (pg. 5674, col. 2, pgph 1). Finally, Martinez-Serrano et al. teaches that the cells expressed a transgene encoded NGF within 500 um of a target cell (pg 5675, Figure 4; pg 5676, Figure 5). Thus, by teaching all the limitations of the claims as written, Martinez-Serrano et al. anticipates the instant invention as claimed.

Claims 1 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Schinstine et al. {Schinstine et al. (1995) Cell Transplant 4:93-102}.

Schinstine et al. provides guidance on a method of administering a therapeutic neurotrophin composition, comprising a cell line transfected with a plasmid encoding human NGF cDNA into the brain of a rodent (Abstract; pg. 94, Materials and Methods). Further, Schinstine et al. teaches that the engrafted cells blocked cholinergic cell loss in fimbria-fornix induced lesions (pg. 99, Figure 4; Pg. 100, Figure 5). Finally, Schinstine et al. teaches that the cells expressed a transgene encoded NGF within 500 um of a target cell (pg 97, Figure 2; pg 98, Figure 3). Thus, by teaching all the limitations of the claims as written, Schinstine et al. anticipates the instant invention as claimed.

Claims 3-15, and 17 are free of the prior art of the record.

No claims allowed

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy J Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Dr. Louis D. Lieto
Patent Examiner
Art Unit 1632

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

JASEMINE C. CHAMBERS
DIRECTOR
TECHNOLOGY CENTER 1600